REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated March 27, 2003 are respectfully requested. Applicants petition the Commissioner for a 1-month extension of time. A Notice of Appeal and Petition for 1-month extension of time accompanies this amendment.

I. Rejections under 35 U.S.C. §102

Claims 29-31, 33-37, 39, and 40-45 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Marshall *et al.* (U.S. Patent No. 5,939,401).

These rejections are respectfully traversed for the following reasons.

A. The Invention

The present invention relates to a method of administering a therapeutic agent entrapped in liposomes formed of vesicle-forming lipids and having a coating of hydrophilic polymer chains on the liposome outer surface via inhalation.

B. The Cited Art

MARSHALL ET AL. relate to cationic amphiphiles complexed with therapeutic molecules for intracellular delivery. A dispersion of the amphiphile is prepared and contacted with a biologically active molecule to forma a complex between the amphiphile and the molecule. Cells are then contacted with the complex to facilitate transfer of the molecules into the cells. The complexes may be administered "by onsite delivery using additional micelles, gels and liposomes." One type of structure that may be formed by amphiphiles is the liposome, however, "owing to the potential for leakage of contents therefrom, vesicles or other structures formed from numerous of the cationic amphiphiles are not preferred by those skilled in the art in order to deliver low molecular weight biologically active materials." When the amphiphile is prepared as a thin-film evaporated from chloroform, "it may be advantageous to prepare the amphiphile-containing film to include one or more further ingredients that act to stabilize the final amphiphile/DNA composition," such as PEG-DMPE.

C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements, M.P.E.P. § 2131.

As embodied by claim 29, the present invention includes administering, via inhalation, liposomes formed of vesicle-forming lipids and having a coating of hydrophilic polymer chains on the liposome outer surface, where said liposomes have an entrapped therapeutic agent.

1. Marshall *et al.* fail to teach a liposome with an entrapped therapeutic agent as in the present invention. The amphiphile of Marshall *et al.* is complexed with the biologically active molecule. While Marshall *et al.* teach that the amphiphiles may form liposomes, Marshall *et al.* in no way teach discrete liposomes with an entrapped therapeutic agent, as in the present invention. The biologically active molecule of Marshall *et al.* is described as polynucleotides, such as genomic DNA, cDNA and mRNA, ribosomal RNA, antisense polynucleotides, and ribozymes, which are complexed with an amphiphile, but are not entrapped due to the large size of the molecule-liposome complexes, charge interactions, and rather poor *in vivo* transfection efficiencies. Further, Marshall *et al.* state that the liposomes formed of the amphiphiles "are not preferred" due to the fact that liposomes formed from the amphiphiles may leak the biologically active molecule.

Examiner's First Assertion: The Examiner asserts that "Marshall's statements...do not exclude the formation of liposomes."

Applicant's Response: While the Applicant realizes that Marshall *et al.* does not exclude liposomes, Marshall *et al.* does not explicitly teach liposomes. More importantly, Marshall *et al.* does not teach liposomes with an entrapped therapeutic agent by the very nature of the biologically active molecules taught by Marshall *et al.*

2. Marshall *et al.* further fail to teach a liposome having a coating of hydrophilic polymer chains on the liposome outer surface. The amphiphile-molecule complex may be formed into a thin-film by chloroform evaporation. The amphiphile-containing film may include PEG-DMPE as a stabilizing ingredient, but no mention is made of a liposome with a coating of hydrophilic polymer chains on the liposome outer surface.

Examiner's Second Assertion: The Examiner asserts that "since Marshall's formulations contain PEG-DMPE...it is implicit that the hydrophilic polymer structures extend outside the surface of the liposomes, and therefore, the outer surface of the liposomes are coated."

Applicant's Reply: Applicants respectfully disagree with this assertion. As noted by the Examiner, Marshall *et al.* simply teaches the use of an amphiphile-containing film that may include PEG-DMPE as a stabilizing ingredient. One of skill in the art would in no way take this as a teaching of a liposome with a hydrophilic polymer coating.

Examiner's Third Assertion: The Examiner further notes that "[i]nstant claims do not require that the coating be continuous over the surface."

Applicant's Reply: Applicants fail to understand how this statement relates to the present application. As noted above, Marshall *et al.* fails to teach a liposome with any hydrophilic polymer coating.

Examiner's Fourth Assertion: The Examiner asserts that "Applicant's arguments that Marshall's formulations do not have a biologically active agent."

Applicant's Reply: The Examiner has apparently misunderstood the Applicant's arguments. Applicants maintain that Marshall *et al.* does not teach an entrapped therapeutic agent.

As the standard for novelty has not been satisfied, withdrawal of the rejections under 35 U.S.C. §102 is respectfully requested.

II. Rejections under 35 U.S.C. §103

Claims 29-30, 34-37, 39-41, 44-49, and 55 were rejected under 35 U.S.C. §103 as allegedly obvious over Mihalko *et al.* (PCT Publication No. WO 86/06959 to Liposome Technology) in combination with Klibanov *et al.* (J. Liposome Research, 2(3):321-334, 1992).

Claims 29-31, 33-37, 39, and 40-45 were rejected under 35 U.S.C. §103 as allegedly obvious over Marshall *et al.* by itself or in combination with Mihalko *et al.*

Claims 31-33 were rejected under 35 U.S.C. §103 as allegedly obvious over Marshall *et al.* by itself or in combination with Mihalko *et al.*, further in view of Gao and Huang (*BBRC*, 179(1):280-285, 1991).

Claims 49-57 were rejected under 35 U.S.C. §103 as allegedly obvious over Mihalko *et al.* in combination with Klibanov *et al.*, further in view of Chestnut *et al.* (U.S. Patent No. 5,800,815), DeFrees *et al.* (U.S. Patent No. 5,604,207) and Applicants' statements of prior art.

These rejections are respectfully traversed.

A. The Invention

The present invention is described above.

B. The Cited Art

MARSHALL ET AL. is described above.

MIHALKO ET AL. describe a method and system for inhalation administration of a drug in a suspension of liposomes, where the liposomes are formulated to produce a selected rate of drug-release from the liposomes. The drug is released from the liposomes by efflux from the liposome. The rate of efflux can be selectively controlled according to the lipid composition of the liposomes. The drug release half-live may range from a half hour or less to six days or more. The drug is predominately entrapped in the liposomes. The system further provides for a device to aerosolize the liposome suspension for inhalation.

KLIBANOV ET AL. disclose coating liposome surfaces with a hydrophilic layer to create long-circulating liposomes. The liposomes are coated with the hydrophilic layer to avoid rapid uptake by the reticuloendothelial system for systemic delivery of the liposomes. The liposomes may further comprise an anti-tumor antibody attached (in one embodiment) to the distal ends of PEG chains on liposomes. The purpose of the attached antibodies is to target the liposomes to a tumor site, for localized delivery of an entrapped drug at the site. The only method of administration described is intravenous.

GAO AND HUANG disclose a cationic cholesterol derivative as a nonviral transfection reagent. Liposomes containing the cationic cholesterol derivative were found to be

more efficient in transfection and less toxic to treated cells as compared to the lipofectin reagent.

CHESTNUT ET AL. disclose compositions and methods for treating inflammation and other conditions using blocking P-selectin antibodies. An anti-P-selectin immunoglobulin may be imbedded in an liposome to target the liposome to P-selectin molecules.

DEFREES ET AL. relate to analogues of sialyl Le^x that inhibit cellular adhesion between a selectin and cells that express sialyl Le^x on their surfaces. Liposomes with an entrapped chemotherapeutic agent can be targeted to a site of tissue injury by the selectin-SLe^x analogue. The analogue is positioned on the surface of the liposome. The liposome is fashioned such that a connector portion is incorporated into the membrane at the time of forming the liposome membrane. The connector portion has a lipophilic portion that is embedded and anchored in the membrane. The liposomes may be administered parenterally or locally.

C. Analysis

As stated in M.P.E.P. § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

1. Rejection over Mihalko *et al.* in combination with Klibanov *et al.*

(a) None of the references, or combination of references provide motivation for combining the references along the lines of the invention. Obviousness requires some logical reason for combining the references at hand; otherwise, the use of the references will entail prohibited hindsight (e.g., Ex parte Stauber 206 USPQ 945; In re Adams 148

USPQ 742; In re Imperato 179 USPQ 730). In particular, the fact that references can be combined does not make the combination obvious unless the prior art also contains something to suggest the desirability of that combination (In re Imperato; In re Semaker, 217 USPQ 1).

To arrive at the claimed invention, one would need to modify the liposomes of Mihalko *et al.* to include a coating of hydrophilic polymer chains.

Motivation to make this modification is simply not found in either Mihalko *et al.* or Klibanov *et al.* Mihalko *et al.* provides no guidance for liposomes having a coating of hydrophilic polymer chains.

Nor is the motivation found in Klibanov *et al.* as this reference is concerned with preparing liposomes containing lipids derivatized with polyethylene glycol to extend systemic circulation of the liposome and prevent uptake by RES (page 324, lines 19-22). Nowhere does Klibanov *et al.* make any mention of other forms of administration much less by inhalation, or that liposomes with a coating of hydrophilic polymers chains would be suitable for administration by inhalation.

Examiner's First Assertion: The Examiner states that to "coat the liposomes of WO 86 with a hydrophilic polymer would have been obvious to one of ordinary skill in the art because such a coating would enable the liposomes to circulate longer and reach the target tissue."

Applicant's Reply: The Examiner appears to have misunderstood the teaching in Mihalko *et al.* As noted above, the liposomes of Mihalko *et al.* are administered by inhalation to the lung. The drug is released from the liposomes into the respiratory tract. The drug is subsequently taken up systemically from the site of deposition in the pulmonary region of the respiratory tract. Nowhere does Mihalko *et al.* teach systemic delivery of the liposome or of the drug in liposome entrapped form. Thus, Mihalko *et al.* does not teach liposomes that circulate systemically, so there is no motivation based on enabling the liposomes to circulate longer.

Examiner's Second Assertion: The Examiner states that "although the administration in Mihalko is by inhalation (just as in instant application), the purpose is to deliver the drug systemically and the inhaled drug in the liposomal formulation enters the blood for circulation".

Applicant's Reply: As described above, the liposomes of Mihalko *et al.* are not delivered systemically. The liposomes of Mihalko *et al.* are formulated to produce a selected rate of drug-release from the liposomes. The drug is released from the liposomes by efflux from the liposome and only the drug enters the blood for circulation. As the purpose of the liposome with a hydrophilic polymer coating is to protect the liposome from the RES for longer circulation, one would not be motivated to modify the liposomes of Mihalko *et al.* as the liposomes do not circulate.

Accordingly, nothing in the teachings of Mihalko *et al.* or Klibanov *et al.* would motivate one skilled in the art to modify the teachings of the references to administer liposomes having a coating of hydrophilic polymer chains by inhalation.

(b) Even if, inter alia, the references provided motivation to combine the teachings along the instant invention, according to M.P.E.P. § 2143, another of the basic criteria to establish a prima facie case of obviousness is that "there must be a reasonable expectation of success." Neither of the references, alone or in combination provide a reasonable expectation of success that liposomes having a coating of hydrophilic polymer chains would be effective for administration by inhalation. Coating a liposome with hydrophilic polymer chains can drastically change the size of the liposome particle which would affect delivery to the lung. One of skill in the art has no way of knowing if these larger particles would get trapped in the upper airway and not even be deliverable to the lung. Further, according to Mihalko *et al.* "[r]educing liposome particle size may be important in achieving efficient aerosolization of the liposomes" (page 13, lines 24-26). As derivatizing the liposomes with a coating of hydrophilic polymer chains increases the particle size, liposomes having a coat of hydrophilic polymer chains may not even aerosolize as required by Mihalko *et al.* There is simply no way of knowing from these references whether liposomes having a hydrophilic polymer coating would be able to be administered by inhalation, much less be effective.

Examiner's Third Assertion: The Examiner states "Applicant's arguments with regard to the sizes of liposomes in Mihalko are not found to be persuasive since the statement on page 14, lines 14-15 indicate the less crucial nature of the liposomal size."

Applicant's Reply: In the above statement, the Examiner fails to consider the teaching of Mihalko *et al.* as a whole. The statement on page 14, lines 14-15 refers only "where liposomes are aerosolized in the form of an aqueous mist." Further, looking at Mihalko *et al.*, the statement additionally recites that "actual liposome size becomes less crucial *to targeting*" (emphasis added). On page 13, lines 22 through page 14, line 10, Mihalko *et al.* teaches the importance of liposome size in "achieving efficient aerosolization of the liposome" as well as for targeting to the upper or lower respiratory-tract regions. One of skill in the art would know the critical nature of the size of the liposomes with regard to effective aerosolization, as recited by Mihalko *et al.*, as well as for proper delivery to the lung.

Accordingly, withdrawal of the rejections under 35 U.S.C. § 103 is respectfully requested.

2. Rejection over Marshall *et al.* by itself or in combination with Mihalko *et al.*

As noted above, Marshall *et al.* fail to teach liposomes having a coating of hydrophilic polymer chains on the liposome outer surface. The teachings in Mihalko *et al.* do not make up for this deficiency as Mihalko *et al.* make no mention of hydrophilic polymer chains or of coating a liposome with hydrophilic polymer chains.

Examiner's Assertion: The Examiner states "[i]t would have been obvious to one of ordinary skill in the art to use this mode of administration of liposomes suggested by Marshall since the mode of administration is the choice of the practitioner."

Applicant's Reply: Applicants respectfully disagree with this assertion. It is well known to one of skill in the art that modes of administration are not interchangable and that each mode has specific difficulties and requirements. In fact, Mihalko *et al.* recites some of the difficulties with other forms of administration in that some drugs "are susceptible to breakdown in the gastrointestinal tract, or which otherwise cannot be administered orally" (page 1, lines 32-34) showing that modes of administration must be chosen carefully based on the limitations of the mode and the therapeutic agent. It is also well known that administration of some drugs by inhalation is simply not feasible. In fact, Mihalko *et al.* states that "[a] related problem is the limitation on the amount of drug that

can be administered safely at each inhalation, particularly in the case of a drug which has unwanted systemic side effects" (page 3, lines 5-9).

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

3. Rejection over Marshall *et al.* by itself or in combination with Mihalko *et al.*, further in view of Gao and Huang

If an independent claim is non-obvious under 35 U.S.C. then any claim depending therefrom is non-obvious. M.P.E.P. §2143.03. The rejection of dependent claims 31-33 relies on Marshall *et al.* by itself, or in combination with Mihalko *et al.*, the deficiencies of which are discussed above. Gao and Huang is cited merely for the inclusion of dimethylaminoethane carbamoyl cholesterol in a liposome formulation. The teaching in Gao and Huang does not make up for the deficiencies in Marshall *et al.* and Mihalko *et al.*, as this reference makes no mention of hydrophilic polymer chains or of coating a liposome with hydrophilic polymer chains.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

4. Rejection over Mihalko *et al.* in combination with Klibanov *et al.*, further in view of Chestnut *et al.* (U.S. Patent No. 5,800,815), DeFrees *et al.* (U.S. Patent No. 5,604,207) and Applicants' statements of prior art

The deficiencies of Mihalko *et al.* and Klibanov *et al.* are discussed above. Chestnut *et al.*, DeFrees *et al.*, and Applicant's statements are cited merely for a teaching of liposomes having a targeting ligand on the surface of the liposome. Neither reference makes any reference to a coating of hydrophilic polymer chains on the liposome outer surface or of administration by inhalation.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

In view of the above remarks, Applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

The Examiner is invited to contact Applicants' representative at 650-838-4410 if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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Date: July 28, 2003

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